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Clinical Research

Duration of Preoperative β-Blockade and Outcomes After Major Elective Noncardiac Surgery

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ABSTRACT

Background: Although practice guidelines recommend that perioperative β-blockade be initiated at least several days to weeks before noncardiac surgery is performed, the minimum required period of preoperative therapy is unclear.

Methods: Population-based administrative databases were used to conduct a cohort study of 48,103 patients aged ≥ 66 years who underwent major elective noncardiac surgery in Ontario, Canada and received preoperative β-blocker therapy. We used multivariable logistic regression to determine the association of duration of preoperative β-blocker treatment (classified as 1-7 days, 8-30 days, and ≥ 31 days) with 30-day mortality, 30-day myocardial infarction (MI), 30-day ischemic stroke, and 1-year mortality.

Results: The duration of preoperative β-blocker treatment was 1-7 days in 1105 patients (2.3%), 8-30 days in 2639 patients (5.5%), and ≥ 31 days in 44,269 patients (92.0%). Compared with ≥ 31 days of preoperative therapy, 1-7 days of therapy was associated with increased 30-day mortality (odds ratio [OR], 1.49; 95% confidence

RÉSUMÉ

Introduction : Bien que les lignes directrices sur la pratique recommandent d'entreprendre le bêtablocage périopératoire au moins plusieurs jours à plusieurs semaines avant la réalisation de la chirurgie non cardiaque, la période minimale requise de traitement préopératoire n'est pas élucidée.

Méthodes : Les bases de données administratives fondées sur la population ont été utilisées pour mener une étude de cohorte de 48 103 patients âgés ≥ 66 ans qui ont subi une chirurgie non cardiaque majeure et non urgente en Ontario, au Canada, et qui ont reçu un traitement bêtabloquant en phase préopératoire. Nous avons utilisé la régression logistique multivariée pour déterminer le lien entre la durée du traitement bêtabloquant en phase préopératoire (classifiée comme allant de 1 à 7 jours, de 8 à 30 jours et ≥ 31 jours), et la mortalité à 30 jours, l'infarctus du myocarde (IM) à 30 jours, l'accident vasculaire cérébral ischémique à 30 jours et la mortalité à 1 an.

Résultats : La durée du traitement bêtabloquant en phase préopératoire a été de 1 à 7 jours chez 1105 patients (2,3 %), de 8 à 30 jours chez

Postoperative cardiac complications affect 2% of the 234 million individuals undergoing surgery worldwide every year.[1,2] One of the earliest recommended approaches for preventing these events was perioperative β-blockade.[3] These recommendations were largely driven by positive results in 2 initial randomized controlled trials (RCTs),[4,5] especially the **D**utch **E**chocardiographic **C**ardiac **R**isk **E**valuation **A**pplying **S**tress **E**chocardiography (DECREASE)-I trial showing substantial cardiac risk reduction with β-blockade.[5]

Notably, these initial results were not replicated by subsequent RCTs.[6-8] Most recently, the **Peri**operative **Is**chemic **E**valuation (POISE) trial demonstrated that although β-blockers reduced perioperative myocardial infarction (MI), this benefit was offset by increased mortality, stroke, and hypotension.[9] Some experts have attributed the discrepancy between early findings and more recent research to differences in the duration of preoperative therapy.[10] In the DECREASE-I trial,[5] participants received ≥ 7 days of preoperative therapy, whereas patients in recent RCTs began therapy between 2 hours and 1 day before surgery.[6-9] Current guidelines therefore recommend initiating β-blockade "well before a planned procedure with careful titration."[11] Nonetheless, there are few studies

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interval [CI], 1.03-2.16; $P = 0.03$], whereas 8-30 days of therapy was not (OR, 0.95; 95% CI, 0.69-1.31; $P = 0.77$). One to 7 days of preoperative therapy was not significantly associated with 1-year mortality (OR, 1.06; 95% CI, 0.84-1.35; $P = 0.62$), 30-day MI (OR, 1.26; 95% CI, 0.92-1.71; $P = 0.15$), or 30-day ischemic stroke (OR, 1.37; 95% CI, 0.64-2.94; $P = 0.41$).

Conclusions: Initiation of β-blocker therapy 1-7 days before noncardiac surgery is associated with increased 30-day mortality. The findings merit further evaluation by randomized trials.

2639 patients (5,5 %) et ≥ 31 jours chez 44 269 patients (92,0 %). Comparativement au traitement préopératoire ≥ 31 jours, le traitement de 1 à 7 jours a été associé à une augmentation de la mortalité à 30 jours (ratio d'incidence approché [RIA], 1,49; intervalle de confiance [IC] à 95 %, 1,03-2,16; $P = 0,03$), tandis que le traitement de 8 à 30 jours ne l'a pas été (RIA, 0,95; IC à 95 %, 0,69-1,31; $P = 0,77$). Le traitement de 1 à 7 jours n'a pas été significativement associé à la mortalité à 1 an (RIA, 1,06; IC à 95 %, 0,84-1,35; $P = 0,62$), à l'IM à 30 jours (RIA, 1,26; IC à 95 %, 0.92-1.71; $P = 0,15$) ou à l'accident vasculaire cérébral ischémique à 30 jours (RIA, 1,37; IC à 95 %, 0,64-2,94; $P = 0,41$).

Conclusions : L'introduction du traitement bêtabloquant de 1 à 7 jours avant la chirurgie non cardiaque est associée à une augmentation de la mortalité à 30 jours. Les résultats méritent une évaluation plus approfondie à partir d'essais aléatoires.

that have evaluated how the duration of preoperative β-blocker treatment influences outcomes.[12,13] We therefore conducted a population-based study to determine the association of duration of preoperative β-blocker treatment with mortality, MI, and acute ischemic stroke after major noncardiac surgery.

Methods

A more detailed description of the methods is presented in the online Supplemental Methods section. After research ethics approval from Sunnybrook Health Sciences Centre, we conducted a retrospective cohort study using the following linked population-based administrative databases: the Discharge Abstract Database of the Canadian Institute for Health Information, the Ontario Health Insurance Plan database, the Registered Persons Database, and the Ontario Drug Benefit database.[14-18] The cohort included all Ontario residents aged ≥ 66 years who underwent any 1 of 16 prespecified elective intermediate- to high-risk noncardiac surgical procedures between April 1, 2003 and March 31, 2009[11,19,20] and received preoperative β-blocker therapy. Such therapy was defined by outpatient prescriptions for oral β-blockers (excluding sotalol, carvedilol, or nadolol) within 100 days before surgery. The included operations were abdominal aortic aneurysm repair, carotid endarterectomy, peripheral vascular bypass, hip replacement, knee replacement, large bowel resection, partial liver resection, pancreatoduodenectomy, pneumonectomy, pulmonary lobectomy, gastrectomy, esophagectomy, abdominal hysterectomy, radical prostatectomy, nephrectomy, and cystectomy. Individuals were classified as having received (1) 1-7 days, (2) 8-30 days, or (3) ≥ 31 days of preoperative β-blocker therapy.[13] We used the prescription closest to the surgical procedure to determine each individual's daily β-blocker dose.

The primary outcome was 30-day mortality, and secondary outcomes included 30-day MI, 30-day acute ischemic stroke, and 1-year mortality. Other covariates included demographic information from the Registered Persons Database, as well as the presence of diabetes and hypertension, which we identified using validated algorithms.[15,17] The Ontario Health Insurance Plan database was used to identify anyone who required dialysis before surgery. Using the Discharge Abstract Database, we identified other comorbidities, including coronary artery disease, heart failure, cerebrovascular disease, peripheral vascular disease, pulmonary disease, renal insufficiency, and malignancy.[21] Perioperative cardiac risk was estimated using the Revised Cardiac Risk Index.[22] The Ontario Drug Benefit database was used to ascertain preoperative prescriptions for calcium channel blockers, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, diuretics, thienopyridines, warfarin, and statins.

All analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC). A 2-tailed P value < 0.05 was used to define statistical significance. We first used appropriate tests (1-way analysis of variance, Kruskal-Wallis test, χ^2 test) to compare the characteristics and outcomes of patients receiving differing durations of preoperative β-blockade. We excluded carotid endarterectomy procedures when performing analyses related to acute ischemic stroke. Multivariable logistic regression modelling was used separately to determine the adjusted association between duration of β-blocker treatment and 30-day mortality, 1-year mortality, 30-day MI, and 30-day ischemic stroke.[9,23,24] Subgroup analyses were performed based on age, sex, and surgical procedure. We also repeated the analyses separately within subgroups receiving either long-acting β-blocker formulations (ie, atenolol, bisoprolol, metoprolol succinate) or other β-blocker formulations. Additionally, multivariable analyses were repeated after categorizing the duration of β-blocker therapy as 1-7 days, 8-14 days, 15-21 days, 22-30 days, and ≥ 31 days. We also used restricted cubic splines to model the association between the duration of preoperative β-blocker treatment and 30-day mortality.[25]

Results

The cohort included 48,013 individuals: 2.3% (n = 1105) began β-blocker therapy within 1-7 days before surgery, 5.5% (n = 2639) began therapy between 8 and 30 days before surgery, and 92.0% (n = 44,269) began therapy ≥ 31 days before surgery. The 3 categories differed with respect to many perioperative characteristics (Table 1), as well as the type (Supplemental Table S1) and daily dose (Supplemental Table S2) of β-blocker. Nonetheless, daily dosage did not differ significantly between individuals receiving 1-7 days vs 8-30 days of preoperative β-blocker therapy (Supplemental Table S2).

Table 1. Characteristics of study cohort*

	Duration of preoperative β-blocker therapy			
	1-7 days before surgery (n = 1105) (%)	8-30 days before surgery (n = 2639) (%)	≥ 31 days before surgery (n = 44,269) (%)	*P* value
Demographics				
Female sex	525 (47.5)	1351 (51.2)	23,169 (52.3)	0.004
Age (y), mean (SD)	75.3 (5.9)	75.4 (6.1)	75.0 (5.9)	0.002
Comorbid disease				
Coronary artery disease	176 (15.9)	429 (16.3)	11,187 (25.3)	< 0.001
Congestive heart failure	26 (2.4)	68 (2.6)	2357 (5.3)	< 0.001
Cerebrovascular disease	35 (3.2)	101 (3.8)	1879 (4.2)	0.13
Peripheral vascular disease	161 (14.6)	438 (16.6)	5494 (12.4)	< 0.001
Atrial fibrillation	33 (3.0)	99 (3.8)	3253 (7.3)	< 0.001
Hypertension	925 (83.7)	2231 (84.5)	40,901 (92.4)	< 0.001
Diabetes mellitus	377 (34.1)	763 (28.9)	13,978 (31.6)	0.003
Pulmonary disease	66 (6.0)	165 (6.3)	2674 (6.0)	0.90
Renal disease	29 (2.6)	93 (3.5)	2231 (5.0)	< 0.001
Malignancy				
Primary	381 (34.5)	653 (24.7)	11,204 (25.3)	< 0.001
Metastatic	82 (7.4)	153 (5.8)	2226 (5.0)	
Procedure				
AAA repair	84 (7.6)	278 (10.5)	2704 (6.1)	
Carotid endarterectomy	28 (2.5)	85 (3.2)	1770 (4.0)	
Peripheral vascular bypass	64 (5.8)	129 (4.9)	2092 (4.7)	
Total hip replacement	173 (15.7)	521 (19.7)	8565 (19.3)	
Total knee replacement	314 (28.4)	876 (33.2)	15,191 (34.3)	
Large bowel surgery	231 (20.9)	339 (12.8)	6506 (14.7)	
Liver resection or pancreatoduodenectomy	16 (1.5)	17 (0.6)	370 (0.8)	< 0.001
Lung resection	25 (2.3)	74 (2.8)	997 (2.3)	
Gastrectomy or esophagectomy	24 (2.2)	31 (1.2)	696 (1.6)	
Abdominal hysterectomy	80 (7.2)	162 (6.1)	2802 (6.3)	
Radical prostatectomy	27 (2.4)	54 (2.0)	990 (2.2)	
Nephrectomy	27 (2.4)	41 (1.6)	1160 (2.6)	
Cystectomy	12 (1.1)	32 (1.2)	426 (1.0)	
Revised Cardiac Risk Index†				
1 point	374 (33.8)	1017 (38.5)	15,663 (35.4)	
2 points	422 (38.2)	1028 (39.0)	16,157 (36.5)	< 0.001
3 points	238 (21.5)	444 (16.8)	8301 (18.8)	
≥ 4 points	71 (6.4)	150 (5.7)	4148 (9.4)	
Preoperative medications				
ACE inhibitor	435 (39.4)	1027 (38.9)	1952 (44.1)	< 0.001
ARB	177 (16.0)	442 (16.7)	814 (18.4)	< 0.001
Calcium channel blocker	150 (13.6)	417 (15.8)	763 (17.2)	< 0.001
Furosemide	101 (9.1)	205 (7.8)	559 (12.6)	< 0.001
Thiazide diuretic	265 (24.0)	648 (24.6)	1133 (25.6)	< 0.001
Statin	471 (42.6)	1146 (43.4)	2234 (50.4)	< 0.001
Thienopyridine	39 (3.5)	93 (3.5)	353 (8.0)	< 0.001
Warfarin	62 (5.6)	186 (7.0)	538 (12.1)	< 0.001

AAA, abdominal aortic aneurysm; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; SD, standard deviation

*Values are expressed as number (percentage) unless indicated otherwise

The overall event rates were 1.7% (n = 839) for 30-day mortality, 6.2% (n = 2954) for 1-year mortality, and 2.9% (n = 1380) for 30-day MI (Fig. 1; Supplemental Table S3). Among the 46,130 individuals who underwent a surgical procedure besides carotid endarterectomy, 0.3% (n = 149) experienced 30-day acute ischemic strokes. Compared with starting β-blocker treatment ≥ 31 days before surgery (Fig. 1), the unadjusted risk of 30-day mortality was significantly higher ($P = 0.005$) among individuals who started therapy 1-7 days before surgery, whereas their unadjusted risk of 1-year mortality approached statistical significance ($P = 0.06$). Their unadjusted risks of 30-day MI ($P = 0.14$) and 30-day ischemic stroke ($P = 0.50$) were not significantly different.

After multivariable risk adjustment (Table 2), initiation of β-blocker therapy 1-7 days before surgery was associated with increased 30-day mortality (odds ratio [OR] 1.49; 95% confidence interval [CI], 1.03-2.16; $P = 0.03$), whereas initiation between 8 and 30 days before surgery was not (OR, 0.95; 95% CI, 0.69-1.31; $P = 0.77$). There was no statistically significant association between duration of β-blocker treatment and other outcomes (Table 2). Kaplan-Meier curves suggested that the additional deaths associated with 1-7 days of preoperative β-blocker therapy were largely observed early after surgery (Fig. 2).

There were no subgroup effects based on age, surgical procedure, or β-blocker type. The relationship between the duration of preoperative β-blocker treatment and 30-day mortality remained similar if treatment duration was modelled using restricted cubic splines (Supplemental Fig. S1), or as a 5-level categorical variable (Supplemental Table S4).

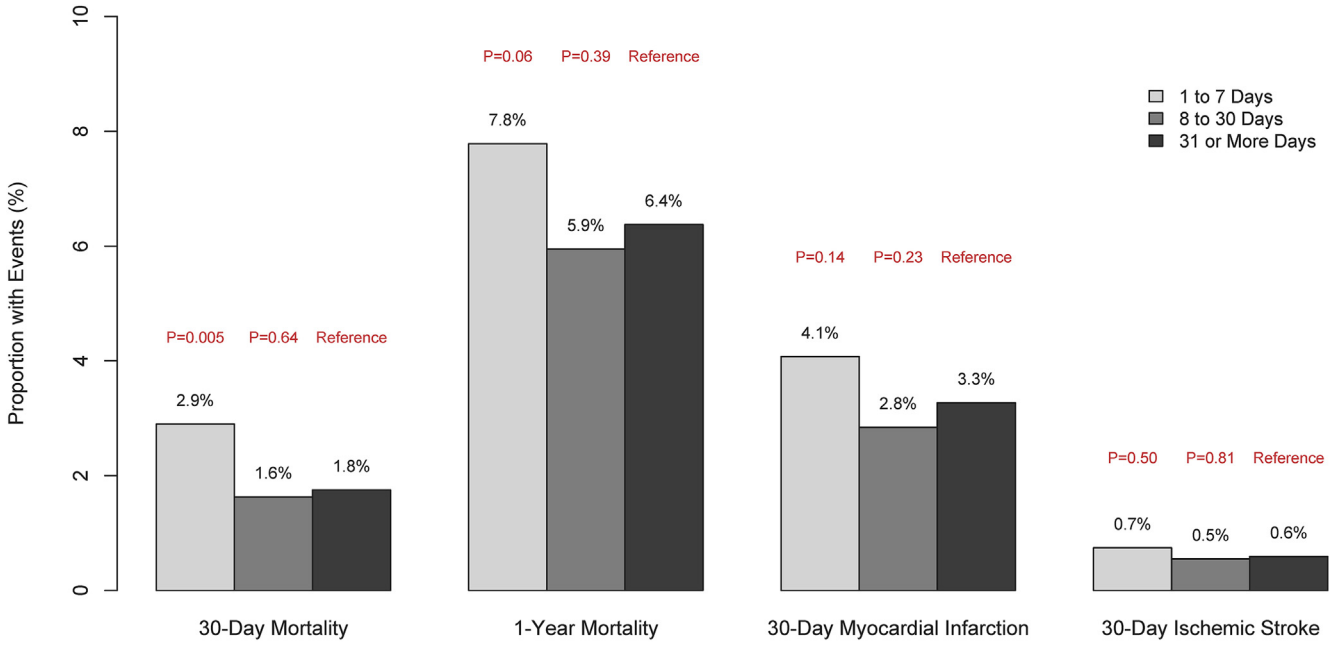

Figure 1. Unadjusted event rates for specific postoperative complications based on the duration of β-blocker treatment before surgery. The *P* values for unadjusted statistical comparisons of proportions with these specific complications are presented in red text above their respective columns.

Discussion

In this population-based study, initiation of oral β-blocker therapy within 1-7 days before major elective noncardiac surgery was associated with increased 30-day mortality. By comparison, once 8-30 days had elapsed after initiation of therapy, the risk of 30-day mortality was not significantly different from that in individuals receiving β-blockers for longer periods. Notably, the timing of preoperative β-blocker initiation appeared to influence only short-term postoperative mortality. Recent initiation of β-blockade had no significant association with 1-year mortality, and additional deaths associated with recent β-blocker initiation were largely observed during the immediate postoperative period.

There are several possible explanations for the increased 30-day mortality among patients who started β-blocker therapy 1-7 days before surgery. First, the decreased time window may not allow for adequate dose titration to simultaneously achieve reasonable heart rate control while minimizing hypotension,[13] although we did not observe differences in β-blocker dosage between individuals receiving 1-7 days vs 8-30 days of preoperative therapy. Second, cardiovascular effects of acute vs chronic β-blocker therapy may differ, as previously demonstrated in patients receiving β-blockers for treatment of hypertension. Dunn et al. demonstrated that although initial acute intravenous β-blocker administration decreased cardiac output and increased peripheral vascular resistance, these changes are attenuated after 4 weeks of ongoing oral therapy.[26] Third, residual unmeasured confounding may have explained, in part, the increased 30-day mortality among individuals who underwent surgery shortly after starting β-blockade therapy. Specifically, our databases lacked some relevant information, such as disease severity or indications for β-blockade. Nonetheless, it is unlikely that unmeasured confounding is the *only* explanation for our findings, especially because it would have also biased the risk of 1-year mortality, which was not increased after 1-7 days of preoperative β-blockade. In contrast, true adverse hemodynamic effects from acute β-blockade could have plausibly affected only 30-day mortality. Indeed, selective effects on short-term vs long-term mortality have been observed for interventions affecting perioperative hemodynamic stability. For example, 30-day mortality is higher after open vs endovascular abdominal aortic aneurysm repair, yet the 2 techniques have similar risks of long-term mortality.[27-29]

Our study warrants comparison with the POISE trial,[9] as well as the 2 previous observational studies.[12,13] Our findings

Table 2. Adjusted association of timing of β-blocker initiation with clinical outcomes

Duration of preoperative β-blocker therapy	30-day mortality	30-day MI	1-year mortality	30-day ischemic stroke
1-7 days before surgery (n = 1105)	OR, 1.49 95% CI, 1.03-2.16 $P = 0.03$	OR, 1.26 95% CI, 0.92-1.71 $P = 0.15$	OR, 1.06 95% CI, 0.84-1.35 $P = 0.62$	OR, 1.37 95% CI, 0.64-2.94 $P = 0.41$
8-30 days before surgery (n = 2639)	OR, 0.95 95% CI, 0.69-1.31 $P = 0.77$	OR, 0.93 95% CI, 0.73-1.18 $P = 0.53$	OR, 0.90 95% CI, 0.75-1.07 $P = 0.22$	OR, 1.14 95% CI, 0.65-2.02 $P = 0.64$
≥ 31 days before surgery (n = 44,269)	Reference	Reference	Reference	Reference

CI, confidence interval; MI, myocardial infarction; OR, odds ratio

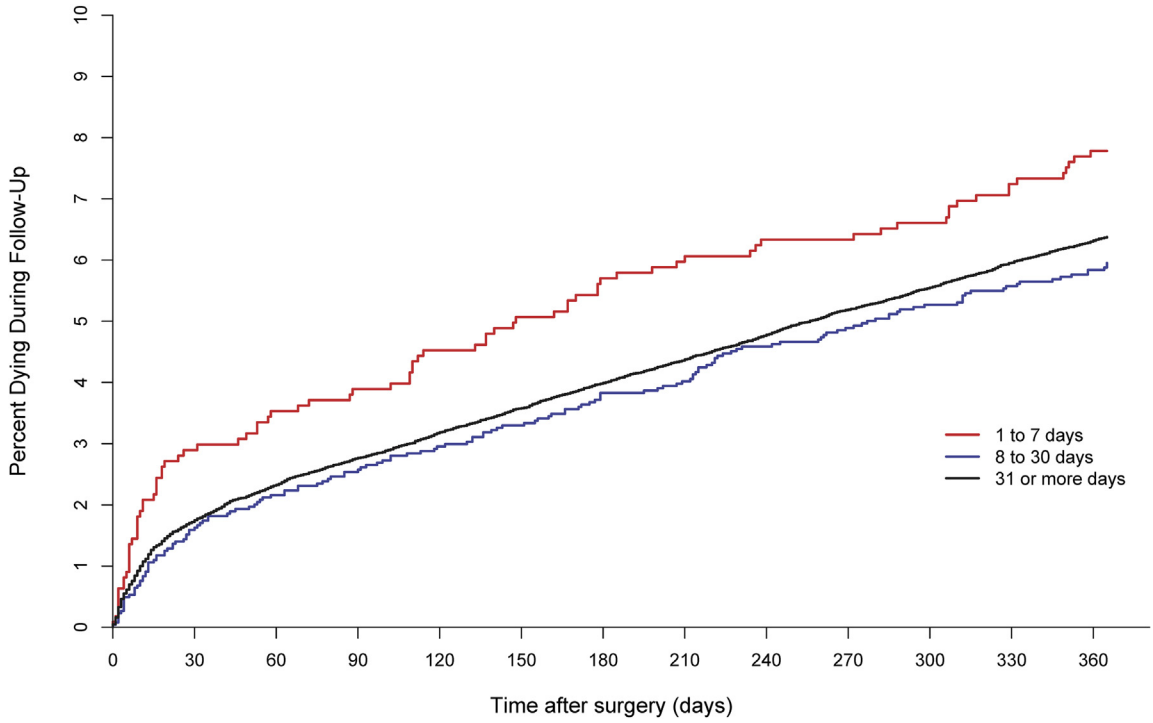

Figure 2. Kaplan-Meier curves describing time to mortality within 1 year after major elective noncardiac surgery stratified by duration of preoperative β-blocker therapy. Percentage of patients dying of all causes among individuals who were receiving β-blocker therapy before major elective noncardiac surgery are seen. The figure represents unadjusted Kaplan-Meier curves for 3 categories defined by the interval from β-blocker initiation to surgery.

have some consistency with the POISE trial with respect to the increased 30-day mortality among patients starting β-blocker therapy immediately before surgery. Conversely, although β-blockers reduced MI in the POISE trial, our adjusted analyses found an *increased* risk of MI that bordered on statistical significance ($P = 0.15$) among individuals receiving 1-7 days of preoperative β-blockade. These seemingly contradictory results may be explained, in part, by differences in the comparisons being made. Specifically, although the POISE trial compared β-blockers against placebo, all individuals in our study were receiving β-blockers, and the comparisons pertained to different timing of β-blocker initiation. To date, there has been no direct randomized comparison of short vs long duration of preoperative β-blocker therapy. Qualitative evaluation of relevant individual RCTs *suggests* the possibility that risks of postoperative MI could be higher after shorter vs longer durations of preoperative β-blocker therapy. For example, when compared with placebo, the POISE trial β-blocker protocol caused a moderate reduction in MI (hazard ratio, 0.73; 95% CI, 0.60-0.89). Conversely, in comparison with open-label control, prolonged periods of preoperative β-blocker therapy caused large reductions in postoperative nonfatal MI or cardiac death in both the DECREASE-I (relative risk, 0.09; 95% CI, 0.02-0.37) and DECREASE-IV (hazard ratio, 0.34; 95% CI, 0.17-0.67) trials.[5,30] Nonetheless, these comparisons should be viewed cautiously because the results of the DECREASE-I and DECREASE-IV trials may be exaggerated because of their use of open-label control[31] and early termination of the trials.[32]

Previous observational studies that directly evaluated the timing of preoperative β-blocker initiation included single-centre cohort studies from the Netherlands and Canada.[12,13] Our findings are consistent with these previous studies in that all studies demonstrated worsened outcomes among individuals who received β-blocker therapy for $<$ 7-10 days before surgery. However, these previous studies had some differences with respect to the types of adverse events seen in patients receiving $<$ 7-10 days of preoperative β-blockade. For example, in the previous studies, mortality rates in this subgroup were not significantly different, whereas rates of postoperative troponin elevation were increased.[13] In our study, such individuals experienced significantly increased rates of 30-day mortality and a possible trend toward increased postoperative MI. These differences may be explained by the increased statistical power for assessing differences in 30-day mortality in our present study and improved ascertainment of MI in the previous cohort studies. Specifically, there were relatively few 30-day deaths in the previous cohort studies, whereas our present analysis included 839 such events. Conversely, the previous cohort studies ascertained MI based on recorded troponin measurements, whereas we relied on less accurate International Classification of Diseases (ICD)-10 diagnostic codes.

Our findings suggest that if β-blocker therapy is deemed warranted in a patient awaiting major elective noncardiac surgery, therapy should preferentially be started $\geq$ 8 days before surgery. Nonetheless, our study does not address whether 8-30 days of therapy is *superior* to no therapy at all,

which is the most clinically relevant question. Although a meta-analysis of high-quality RCTs has shown that preoperative β-blockade, regardless of its duration, reduces the risk of MI,[33] the dilemma that clinicians face is the potential for associated increases in perioperative mortality and stroke. The consistency of findings in our present analysis and previous cohort studies point to the need for an adequately powered placebo-controlled RCT to determine whether a moderate and clinically feasible duration of titrated preoperative β-blocker therapy (ie, $\geq$ 8 days) can achieve a reduction in MI without simultaneous increases in mortality or acute stroke. Such a trial is urgently needed, especially because perioperative MI remains frequent and prognostically important,[34] β-blockers do reduce the risk of these complications,[9,33] and β-blockers remain an easily accessible cardiovascular medication for most perioperative clinicians.

Several limitations of our study should be considered. First, in-hospital β-blocker use was not captured by our databases. Thus, we were not able to assess whether patients continued to receive β-blocker therapy during their hospital stays. In addition, our analysis excluded individuals who started β-blocker therapy immediately before surgery after hospital admission. Nonetheless, such regimens have already been evaluated by the POISE trial. Second, despite the large sample size of this multicentre study, its statistical power to address some relevant questions was limited. For example, we could not further categorize the subgroup of patients with 1-7 days of preoperative β-blocker therapy to determine the risks associated with even shorter periods of preoperative β-blocker therapy. In addition, the low incidence of postoperative ischemic stroke limited statistical power to compare different durations of preoperative β-blocker treatment with respect to risks of this important complication. Notably, the overall number of strokes within the cohort (n = 218) meant that estimates from the relevant regression model were *not biased*. The ratio of outcome events—to—predictor variables within the model exceeded the minimum 10:1 ratio recommended to minimize bias when estimating coefficients in logistic regression models.[35] Nonetheless, the low absolute number of ischemic strokes among individuals who received $<$ 31 days of preoperative β-blocker therapy resulted in associated odds ratios with wide and imprecise confidence intervals. Third, our data sources did not capture some relevant detailed clinical information. For example, the databases did not capture physiologic information (eg, heart rate), laboratory test results, specific postoperative complications (eg, hypotension), or causes of death, all of which might have provided insights into the mechanisms whereby very recent initiation of preoperative β-blocker therapy led to increased 30-day mortality. Fourth, as with any observational study, our study by itself does not prove a causal relationship between a very short period of preoperative β-blocker therapy and increased 30-day mortality. Our hypothesis-generating findings therefore warrant confirmation by other multicentre observational studies, as well as definite evaluation in an adequately powered RCT.

Conclusions

In this population-based study, initiation of oral β-blocker therapy within $\leq$ 7 or days before major elective noncardiac surgery was associated with significantly increased 30-day mortality. In concert with similar findings in previous cohort studies, these present findings point to the need for a multicentre placebo-controlled RCT to determine whether a moderate duration of preoperative β-blocker therapy (ie, $\geq$ 8 days), which is titrated to an optimal dose, can prevent perioperative cardiac complications, mortality, and acute stroke.

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Disclosures

The authors have no conflicts to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2013.10.011.